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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
EPPERSON, JON D	
ART UNIT	**PAPER NUMBER**
1639	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/824,743	THURSTON ET AL.	
	Examiner	Art Unit	
	Jon D. Epperson	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 July 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *26-36 and 38-47* is/are pending in the application.

4a) Of the above claim(s) *26-35 and 41-46* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *36 and 38-40* is/are rejected.

7)☒ Claim(s) *47* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

Status of the Application

1. The Response filed July 19, 2007 is acknowledged.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior office action.

Status of the Claims

3. Claims 26-46 were pending. Applicants amended claim 36, canceled claim 37 and added claim 47. Therefore, claims 26-36 and 38-47 are currently pending. Claims 26-35 and 41-46 are drawn to non-elected species and/or inventions and thus these claims remain withdrawn from further consideration by the examiner, 37 CFR 1.142(b), there being no allowable generic claim. Therefore, claims 36, 38-40 and 47 are examined in this action.

4. This application contains claims 26-35 and 41-46 drawn to a nonelected invention(s). This was addressed in the previous action (see 7/31/06 office action). A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144). See MPEP § 821.01.

Withdrawn Objections/Rejections

5. The objection to the title is withdrawn in view of Applicants' amendments thereto. The

objection to claim 36 is withdrawn in view of Applicants' amendments thereto. The 35 U.S.C. § 112, second paragraph rejections denoted "A" and "B" are withdrawn in view of Applicants' amendments to claim 36 and cancellation of claim 37. The 35 U.S.C. § 112, first paragraph rejection is withdrawn in view of Applicants' amendment to claim 36 and cancellation of claim 37. All other rejections are maintained and the arguments are addressed below.

Outstanding Objections and/or Rejections

Claim Rejections - 35 USC § 103

6. Claims 36 and 38-40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bi et al. (Bi et al. "Building Blocks for peptide and carbamate libraries" *Bioog. & Med. Chem. Lett.* **1996**, *6(19)*, 2299-2300) (3/10/05 IDS) in view of Lescrinier et al. (Lescrinier et al. "DNA-Binding Ligands from Peptide Libraries Containing Unnatural Amino Acids" *Chem. Eur. J.* **1998**, *4(3)*, 425-433) (3/10/05 IDS) and Leber et al. (Leber et al. "A Revised Structure for Sibiromycin" J. Am. Chem. Soc. 1988, 110, 2992-2993) (3/10/05 IDS) and Suggs et al. (Suggs et al., "Synthesis and Structure of Anthramycin Analogs via Hydride Reduction of Dilactams" *Tet. Lett.* **1985**, *26(40)*, 4871-4874) (3/10/05 IDS) and Gordon et al. (Gordon et al., "Application of Combinatorial Technologies to Drug Discovery. II." *J. Med. Chem.* **1994**, *37(10)*, 1385-1401) and Gallop et al. (Gallop et al., "Applications of Combinatorial Technologies to Drug Discovery. I." *J. Med. Chem.* **1994**, *37(9)*, 1233-1251).

For ***claims 36***, Bi et al. (see entire document) teach building blocks for peptide and carbamate libraries (e.g., see abstract), which reads (in part) on the current invention. For example, Bi et al. disclose the same tricyclic ring system (e.g., see Bi et al.,

compound 6 wherein a dihydro-1H-pyrrolo[2,1-c][1,4]benzodiazepine is disclosed). Bi et al. also disclose "hydrogen" at positions R_3 and R_{6-9} positions and a "carbonyl" at position C_5 (e.g., see compound 6) that falls within the scope of the current claims.

The prior art teachings of Bi et al. differ from the claimed invention as follows:

For ***claims 36, 38-40***, Bi et al. fail to teach a C-S, C-O or C-NH bond at the C_{11} position. Bi et al. only teach the use of C=O (e.g., see Bi et al., page 2299, compound 6). Bi et al. also fail to teach the use of a solid support at the N_{10} position or a "combinatorial" unit at R_2 or the actual formation of a combinatorial library (i.e., a collection of compounds).

However, the combined references of Lescrinier et al., Leber et al., Suggs et al., Gordon et al., and Gallop et al. teach the following limitations that are deficient in Bi et al.:

For ***claim 36***, the combined references of Lescrinier et al., Leber et al., Suggs et al., Gordon et al., and Gallop et al. (see entire document) teach the incorporation of unnatural amino acids, like the unnatural amino acid disclosed by Bi, into a peptide library bound to a solid support (e.g., see Lescrinier et al., abstract; see also scheme 1 and Table 1). Incorporation of benzodiazepine "unnatural" amino acids as disclosed by Bi et al. into the DNA-binding peptide library as disclosed by Lescrinier et al. would result in the requisite substitutions at the N_{10} and R_2 positions (e.g., i.e., a solid support with a linking group for N_{10} and a natural or unnatural peptide unit for R_2 wherein A is NH, Y is substituted alkyl (i.e., the backbone of the Cα(R)-C(=O) portion of first attached amino acid is the alkyl which is substituted with O, etc.), X' is NH, and T is the next amino

acid(s), respectively). The combined references of Lescrinier et al., Leber et al., Suggs et al., Gordon et al., and Gallop et al. also teach the use of OH, OCH_3 and SPh groups at the C11 position (e.g., see Leber et al., compounds 3 and 4; see also page 2992, column 1, paragraph 1; see also Suggs et al., page 4871, last paragraph; see also scheme on bottom of page 4872 showing facile conversion of the "dione" using $NaBH_4$ in the first step), which fall within the scope of the current claims.

For ***claim 38***, the combined references of Lescrinier et al., Leber et al., Suggs et al., Gordon et al., and Gallop et al. disclose the formation of a peptide bond (once the unnatural amino acid disclosed by Bi et al. is incorporated into the library), which reads on A = NH, Y is the divalent -C(=O)-CH_2- portion of the adjacent amino acid, X' is the NH portion of the adjacent amino acid and T is the remainder of the peptide (e.g., see Lescrinier et al., page 426, Table 1 wherein any of the disclosed amino acids C-terminus amino acids can be replaced by the unnatural benzodiazepine skeleton; note also that any other peptide library could also be used and screened).

For ***claims 39 and 40***, the combined references of Lescrinier et al., Leber et al., Suggs et al., Gordon et al., and Gallop et al. disclose, for example, compound 1 (e.g., see Lescrinier et al., Table 1) wherein substation of the Alanine would provide n = 4). In this scenario, amino acid number 1 = the unnatural benzodiazepine, amino acid number 2 forms the A-Y-X' as set forth above and amino acids numbers 3-6 represent the four combinatorial units.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to substitute the benzodiazepine "unnatural" amino acid

disclosed by Bi et al. into the DNA-Binding peptide library disclosed by Lescrinier et al. to replace any one of the natural or unnatural amino acids set forth therein because Bi et al. explicitly state that these unnatural amino acids should be used for combinatorial synthesis (e.g., see Bi et al., page 2299, We report here the synthesis of ... benzodiazepine pharmacophore for use in the synthesis of peptide ... combinatorial libraries"), which would encompass the combinatorial libraries disclosed by Lescrinier. Furthermore, a person of skill in the art would have been motivated to use the unnatural amino acids disclosed by Bi et al. because, according to Bi et al., "Amino acids that incorporate pharmacophores are particularly attractive for the synthesis of combinatorial libraries ... [and] benzodiazepine skeleton has been found [to possess] ... a wide range of biological[ly] acitv[ity]" (e.g., see Bi et al., page 2299, paragraph 1). In addition, the tricyclic pyrrolo[1,4]benzodiazepine group is known to possess DNA-binding activity (e.g., see Suggs et al., page 4871, paragraph 1, "The pyrrolo[1,4]benzodiazepine group ... is one of the most interesting classes of DNA-binding drugs"; see also Leber et al., page 2992, column 1, paragraph 1), which is exactly what Lescrinier is screening for (e.g., see Lescrinier et al., abstract, "An unnatural peptide-based library, bound on a solid support was screened for double-stranded-DNA (dsDNA)-binding ligands." Furthermore, a person of skill in the art would reasonably have expected to be successful because benzodiazepine skeleton has been previously used in a "combinatorial format" (e.g., see Bi et al., page 2299, paragraph 1; for more support see also Gordon et al., figure 17; see also Gallop et al., page 1240, section c, establishing high skill level for peptide libraries). In addition, Lescrinier et al. teach that "unnatural" amino acids (like the one disclosed by

Bi et al.) can be easily incorporated into a peptide library (e.g., see Lescrinier et al., Results and Discussion). Finally, Suggs et al. teach a facile synthesis for converting the "dione" skeleton into the OH or SPh groups using simple NaBH4 reduction (e.g., see Suggs et al., scheme on bottom of page 4872).

Response

7. Applicant's arguments directed to the above 35 U.S.C. § 103(a) rejection were fully considered (and are incorporated in their entirety herein by reference) but were not deemed persuasive for the following reasons. Please note that the above rejection has been modified from it original version to more clearly address applicants' newly amended and/or added claims and/or arguments.

[1] Applicants argue, "The sheer number of references necessary to make the alleged obviousness rejection point toward the non-obviousness of the claimed libraries and the use of impermissible hindsight" (e.g., see 7/19/07 Response, pages 10 and 11, especially page 11, middle paragraph).

[1] The Examiner respectfully disagrees. In response to Applicants' argument that the Examiner has combined an excessive number of references, it has been held that the number of references does not have a bearing on the propriety of the rejection; theoretically such could be infinite. *Ex parte Fine* 1927 C.D. 84 (1926).

[2] Applicants argue, "there is no suggestion or motivation ... to modify or to combine the references" (e.g., see 7/19/07 Response, page 11, last paragraph).

[2] In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, a person of skill in the art would have been motivated to use the unnatural amino acids disclosed by Bi et al. because, according to Bi et al., "Amino acids that incorporate pharmacophores are particularly attractive for the synthesis of combinatorial libraries ... [and] benzodiazepine skeleton has been found [to possess] ... a wide range of biological[ly] acitv[ity]" (e.g., see Bi et al., page 2299, paragraph 1). In addition, the tricyclic pyrrolo[1,4]benzodiazepine group is known to possess DNA-binding activity (e.g., see Suggs et al., page 4871, paragraph 1, "The pyrrolo[1,4]benzodiazepine group ... is one of the most interesting classes of DNA-binding drugs"; see also Leber et al., page 2992, column 1, paragraph 1), which is exactly what Lescrinier is screening for (e.g., see Lescrinier et al., abstract, "An unnatural peptide-based library, bound on a solid support was screened for double-stranded-DNA (dsDNA)-binding ligands."

[3] Applicants argue that the examiner has used impermissible hindsight (e.g., see 7/19/07 Response, page 11, bottom paragraph).

[3] In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on

obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

[4] Applicants argue, "the compounds of Bi et al. cannot form an imine bond" (e.g., see 7/19/07 Response, page 12, paragraph 1).

[4] In response to applicant's arguments against the Bi et al. reference individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

[5] Applicants argue, "There is no teaching or suggestion in Lescrinier et al. regarding pyrrolobenzodiazepines" (e.g., see 7/19/07 Response, page 12, paragraph 2).

[5] In response to applicant's arguments against the Lescrinier et al. reference individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

[6] Applicants argue, "Gallop et al. and Gordon et al. ... do not teach ... pyrrolobenzodiazepine libraries of the present invention" (e.g., see 7/19/07 Response, page 12, paragraph 2).

[6] In response to applicant's arguments against the Gallp/Gordon reference(s) individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

[7] Applicants argue, "Leber et al. ... does not teach ... formation of pyrrolobenzodiazepine libraries" (e.g., see 7/19/07 Response, page 12, paragraph 2).

[7] In response to applicant's arguments against the Leber et al. reference individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

[8] Applicants argue, Suggs et al. ... does not teach ... pyrrolobenzodiazepine libraries" (e.g., see 7/19/07 Response, page 12, paragraphs 2 and 3).

[8] In response to applicant's arguments against the Suggs et al. reference individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Accordingly, the 35 U.S.C. § 103(a) rejection cited above is hereby maintained.

Allowable Subject Matter

8. No claims are allowed. However, claim 47 would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. Claim 47 is currently objected to as being dependent upon a rejected base claim.

Conclusion

Applicant's amendment necessitated any new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon D Epperson whose telephone number is (571) 272-0808. The examiner can normally be reached Monday-Friday from 9:00 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James (Doug) Schultz can be reached on (571) 272-0763. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Jon D. Epperson/
Primary Examiner, AU 1639